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Prolonged release oxycodone/naloxone for the treatment of severe pain in patients with Parkinson's disease: PANDA - a double-blind, randomized, placebo-controlled study

Claudia Trenkwalder MD[1], K Ray Chaudhuri DSc FRCP[2], Pablo Martinez-Martin MD[3], Olivier Rascol MD[4], Reinhard Ehret MD[5], Martin Vališ PhD[6,7], Maria Sátori MD[8], Anna Krygowska-Wajs MD[9], Maria J Marti MD[10], Karen Reimer MD[11,12], Alexander Oksche MD[11, 13], Mark Lomax MSc[14], Julia DeCesare MSc[14], and Michael Hopp MD[11] for the PANDA Study Group*

1. Paracelsus-Elena Hospital, Kassel, Germany and Department of Neurosurgery, University Medical Centre, Goettingen, Germany; 2. NFP Parkinson's Centre of Excellence, King's College Hospital, and Biomedical Research Unit for Dementia, King's College, London, United Kingdom; 3. National Centre of Epidemiology, Carlos III Institute of Health, Avda. Monforte de Lemos 5, 28029 Madrid, Spain; 4. Clinical Investigation Centre CIC 1436, INSERM and University Hospital, Toulouse, France; 5. Neurologie Berlin, Gemeinschaftspraxis, Berlin, Germany; 6. Poliklinika Chocen Neuro, Chocen, Czech Republic; 7. Department of Neurology, Faculty of Medicine in Hradec Králové and University Hospital Hradec Králové, Hradec Králové, Czech Republic; 8. Department of Neurology, Vaszary Kolos Hospital, Esztergom, Hungary; 9. Department of Neurology, Jagiellonian University, Botaniczna 3, 31-503, Cracow, Poland; 10. Parkinson's Disease and Movement Disorders Unit, Department of Neurology, Hospital Clinic, CIBERNED, Villarroel 170, Barcelona 08036, Spain; 11. Mundipharma Research GmbH & Co. KG, Höhenstraße 10, 65549 Limburg an der Lahn, Germany; 12. Private University Witten/Herdecke GmbH, Faculty of Health, Alfred-Herrhausen-Straße 50, Witten, Germany; 13. Rudolf-Buchheim Institute of Pharmacology, JLU Giessen, Germany; 14. Mundipharma Research Ltd, Cambridge Science Park, Milton Road, Cambridge, United Kingdom.

*Principle investigators are listed at the end of this paper

Corresponding author

Claudia Trenkwalder
Paracelsus-Elena Hospital
Centre of Parkinsonism and Movement Disorders
Klinikstrasse 16, 34128
Kassel,
Germany
Telephone: +49 561 6009200
Email: ctrenkwalder@gmx.de

Summary

Background: Pain is a frequent non-motor symptom (NMS) of Parkinson's disease (PD). We investigated the analgesic efficacy of prolonged release oxycodone–naloxone (OXN PR) for PD patients with chronic, severe pain.

Methods: This Phase II study was conducted in 47 secondary care centres (Czech Republic, Germany, Poland, Hungary, Romania, Spain and UK; EudraCT 2011-002901-31, ClinicalTrials.gov NCT01439100; trial closed). Patients (Hoehn and Yahr Stage II–IV PD, ≥1 type of severe pain, average 24-h pain score ≥6 [11-point scale]) were randomised (1:1) using a validated, automated system (block size 4) to double-blind oral OXN PR or placebo for 16 weeks (starting dose 5 mg oxycodone /2·5 mg naloxone twice daily). Personnel involved in the study conduct and interpretation were blinded to treatment assignment. Primary endpoint was the superiority of OXN PR vs placebo for average 24-h pain scores (assessed on an 11-point numerical rating scale: 0 = no pain to 10 = pain as bad as you can imagine) at Week 16 in the full analysis population (FAP).

Findings: Of 93 and 109 patients randomised to OXN PR and placebo, respectively, the FAP comprised OXN PR n=88, placebo n=106. Primary endpoint in the FAP was not met: OXN PR least squares (LS) mean (95% CI) 5·0 (4·5, 5·5), placebo 5·6 (5·1, 6·0); LS mean difference (95% CI) -0·6 (-1·3, 0·0), p=0·058. Overall incidences of all-causality adverse events (60/92 [65·2%] vs 76/109 [69·7%]), treatment-related adverse events (52/92 [56·5%] vs 62/109 [56·9%]) and serious adverse events (5/92 [5·4%] vs 7/109 [6·4%]) were comparable between OXN PR and placebo groups. Treatment-related events observed more frequently with OXN PR vs placebo were nausea (16/92 [17·4%] vs 10/109 [9·2%] patients) and constipation (16/92 [17·4%] vs 6/109 [5·5%] patients).

Interpretation: Although the primary endpoint, based on the FAP, was not met (p=0·058), this study adds to current understanding of the potential for opioid-based treatment for patients with PD-related pain and warrants further research investigating the role of OXN PR in this setting.

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Introduction

In addition to the cardinal motor symptoms of Parkinson's disease (PD), non-motor symptoms (NMS) are highly prevalent yet often underreported [1]. NMS, which include gastrointestinal symptoms, neuropsychiatric symptoms, sleep disorders, visual dysfunction, hyposmia and pain, can have a substantial impact on patients' quality of life [1-4]. As with motor symptoms, patients often experience worsening in some NMS when the effects of antiparkinsonian therapy are wearing off [1,4].

PD-related pain affects approximately 60% of patients with PD, and patients frequently report multiple pain types [5-7], which may include musculoskeletal, central or visceral, nocturnal, orofacial, and peripheral limb and abdominal pain [1]. PD-related pain may be attributed to peripheral pain mechanisms, including motor symptoms causing or amplifying pain, and PD pathophysiology in pain processing [8]. Pain in PD is a complex complaint and there is little awareness of the different types of

PD-related pain from both medical and patient perspectives. PD-related pain is commonly only treated by increasing the doses of dopaminergic therapy.

Although PD-related pain is more frequent and more intense than other pain observed in the general population, it is largely undertreated [6,7,9]. Patients with PD-related pain are less likely to be prescribed analgesic therapy compared with individuals with chronic pain-related diseases such as osteoarthritis [6,7,10]. The reasons for this discrepancy are largely unknown, and treatment guidelines for PD-related pain are currently lacking due to an absence of randomised, controlled trials specifically investigating analgesia in this setting [8,11,12]. Given the complexity of PD pain, and the variety of other NMS that patients with PD frequently experience, studies are needed to ascertain the effectiveness and tolerability of different analgesic agents across the spectrum of PD pain types.

World Health Organization Step-3 opioid analgesics are widely used to treat moderate-to-severe pain conditions of various origin[13]. The pain pathways mediated by dopaminergic and opioidergic neurons lie in close proximity in the spinal cord pain transmission pathways and may explain the potential role of opiates in alleviating PD-related pain.Some side effects of opioids overlap with PD symptoms, for example, constipation [14,15]. Opioid-induced constipation arises from the interaction of exogenous opioids with enteric μ-opioid receptors located throughout the gastrointestinal tract [16]. To address gastrointestinal opioid class effects, oxycodone was combined with naloxone, an opioid-receptor antagonist in a prolonged-release formulation (OXN PR). Oral naloxone has negligible systemic availability due to extensive first-pass hepatic metabolism, and has been shown to normalise delayed gastrointestinal transit observed with oxycodone alone [17,18]. OXN PR is marketed worldwide and its efficacy and safety have been demonstrated in a variety of non-malignant and cancer-related pain settings [19-26]. Furthermore, OXN PR at low doses (oxycodone 5·0 mg / naloxone 2·5 mg) has also been shown to provide effective, symptomatic relief of severe restless legs syndrome, and OXN PR at doses of oxycodone 10·0 / naloxone 5·0 mg has demonstrated efficacy for chronic pain in a small prospective study of PD patients [27,28].

This study investigated the analgesic efficacy of OXN PR vs placebo in patients with chronic, severe PD-related pain, and assessed the tolerability of OXN PR and its effect on motor symptoms, NMS, quality of life and intake of rescue medication.

Methods

Study design and participants

This Phase II study comprised 16-week, randomised, double-blind treatment with OXN PR or placebo, followed by a 4-week extension phase of open-label OXN PR aimed to transition patients to subsequent pain treatment at study end (Figure 1). It was performed in 47 secondary care centres in the Czech Republic, Germany, Poland, Hungary, Romania, Spain and UK. The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization Guidelines for Good Clinical Practice and the European Union Clinical Trials Directive. Procedures were approved by local ethics committees, and all patients provided informed, written consent prior to any screening or study enrolment procedures being undertaken.

Patients were ≥25 years and had Hoehn and Yahr Stage II–IV PD, an average 24-h pain score of ≥6 on an 11-point numerical rating scale (NRS; over the 7 days prior to randomisation [29]), severe pain in ≥1 subsection of the Chaudhuri and Schapira pain classification system (now developed and published as the validated King's PD Pain Scale [30,31]) and were considered likely to benefit from WHO Step 3 opioid therapy. Patients also received stable treatment for PD for ≥4 weeks prior to randomisation and did not have visual or auditory disturbances that may prevent them from completing study questionnaires. Women <1 year post-menopause were not pregnant or lactating and willing to use effective contraception throughout the study. Exclusion criteria included severe cognitive impairment or dementia (score of ≤24 on Mini Mental State Examination); history of psychosis (including hallucinations and delusions), drug or alcohol abuse; regular use of opioid-containing mediation in the prior 6 months; and contraindications to OXN PR or rescue medication (levodopa [L-DOPA] / benserazide hydrochloride tablets). Patients were also excluded with medical history or abnormal laboratory/electrocardiogram (ECG) parameters considered to place them at risk upon exposure to study medication. Please see the supplementary appendix for a full list of inclusion and exclusion criteria.

Randomisation and masking

Current antiparkinsonian medications were continued throughout the study. Patients were randomised 1:1 using blocking methodology (block size of 4) to OXN PR or matching placebo. Randomisation was conducted by the Sponsor in a centre-based scheme using a validated automated system (RPAS) that randomly assigned treatment groups to random numbers. Interactive response technology (IRT) was used to manage randomisation and study medication supply. During double-blind treatment, all patients and personnel involved in the conduct and interpretation of the study were blinded to treatment assignment. Treatment allocations were kept blind until the study was completed and after final clinical database lock, except in cases of emergency.

Procedures

Patients attended the study clinic at baseline (randomisation) and at Weeks 1, 2, 4, 8, 12, 16 (end of double-blind treatment/ start of open-label OXN PR phase), 18, and 20 (end of open-label phase; Figure 1). A safety follow-up was conducted 7–10 days after the last dose of study medication. Telephone calls were also conducted on Days 2, 4, 114, and 116 to check if pain scores indicated a need for up-titration of study medication, alertness, use of rescue medication, concomitant medication, changes in PD medication and to record adverse events.

Titration of oral study medication (starting dose 5 mg oxycodone /2·5 mg naloxone twice daily, titrated up to 20/10 mg twice daily, according to the investigator's opinion) was permitted at any time during double-blind treatment if pain was not adequately controlled (L-DOPA / benserazide hydrochloride tablets 100/25 mg were permitted ≤3 times/day).

Vital signs, adverse events, compliance with study medication and use of PD medication, concomitant medications and rescue medication were assessed at each study visit. Study

questionnaires detailed below were also assessed at each study visit with the exception of ≥1 of 9 symptoms in the Wearing off Questionnaire (WOQ-9; assessed at baseline, Weeks, 4, 8, 12, 16, and end of open-label treatment), Parkinson Disease Questionnaire-8 (PDQ-8, assessed at baseline, Week 16 and end of open-label treatment), EQ-5D-3L (assessed at baseline, Week 16 and end of open-label treatment), and Hospital Anxiety and Depression Scale (HADS, assessed at baseline, Weeks 12, 16, and end of open-label treatment). Patient diaries for average 24-h pain score were completed in the 7 days prior to randomisation until Week 2, and for the 7 days preceding study visits thereafter. Clinical laboratory tests and 12-lead ECGs were assessed at screening, Week 16 and end of open-label-treatment.

Outcomes

The primary endpoint was to demonstrate the superiority of OXN PR vs placebo for average 24-h pain scores in the 7 days preceding Week 16 of double-blind treatment. Average 24-h pain was assessed on an 11-point NRS (0 = no pain to 10 = pain as bad as you can imagine) in patient diaries [29]. Secondary endpoints included average 24-h pain scores in the 7 days preceding other study visits during double-blind treatment; percentage of responders (≥30% reduction from baseline) in average 24-h pain at Week 16; and percentage of responders ('much improved' or 'very much improved', assessed on a 7-point scale: 1 = 'very much improved' to 7 = 'very much worse') for Clinical Global Impression-Improvement (CGI-I) at Week 16.

Exploratory efficacy endpoints included percentage of responders (assessed per CGI-I) for Patient Global Impression-Improvement (PGI-I) at Week 16, and change from baseline to Week 16 in NMS Scale for PD (NMSS) total score and domain scores (NMSS item 27 [unexplained pain] was not assessed due to the use of more specific PD-related pain tools in this study). Change from baseline to Week 16 was also assessed for: total scores of the Parkinson's Disease Sleep Scale-2 (PDSS-2), Clinical Impression of Severity Index – Parkinson's Disease (CISI-PD), PDQ-8, Euro-Quality of Life EQ-5D-3L index score, anxiety and depression domains of HADS, Unified Parkinson's Disease Rating Scale (UPDRS) part III (motor examination) and part IV (complications of therapy in the last week). Change from baseline in the percentage of patients meeting WOQ-9 and use of L-DOPA / benserazide hydrochloride rescue medication were also assessed. A post-hoc analysis was conducted to investigate changes in the PD pain subtypes, assessed using the King's Parkinson's Disease Pain Scale [31]. Please see the supplementary appendix for further details of the efficacy endpoints.

Statistical analyses

In total, 210 patients were planned to be randomised to account for drop-outs and provide 86 patients per treatment group in the full analysis population (FAP), which was considered sufficient to detect a treatment difference of 1 point in the primary endpoint (standard deviation [SD] 2 points) with 90% power and 2-sided α-level of 0·05.

Changes in average 24-h pain scores were assessed using a Mixed Model Repeated Measures (MMRM) analysis, including treatment and visit as fixed effects, baseline averaged pain scores as a covariate, treatment by visit and baseline averaged pain score by visit as interactions and centre as a random effect. The primary endpoint was analysed in the FAP (patients who received ≥1 dose of study medication and had ≥1 post-baseline primary efficacy endpoint), with sensitivity analyses performed in the per-protocol population (PPP; patients who complied sufficiently with the study protocol). A hierarchical testing strategy was used to permit confirmatory claims to be made (following the pre-specified hierarchy) in the event of the primary time point being statistically significant. The safety population comprised all patients who received ≥1 dose of study medication.

Responders for average 24-h pain, CGI-I and PGI-I, and percentage of patients meeting WOQ-9 were analysed using logistic regression, including terms for treatment and centre as factors, and baseline average pain score as a covariate. Differences in the use of L-DOPA / benserazide hydrochloride tablets were tested using Wilcoxon Rank Sum test. Other exploratory efficacy endpoints were analysed using ANCOVA, with treatment as a factor, baseline score as a covariate and centre as a random effect. Statistical analyses were performed using SAS® version 9.3 (SAS Institute, Cary, NC, USA) and were overseen by ML, on behalf of the Study Steering Committee (SSC) as there was no separate Data Monitoring Committee. Based on guidance from the SSC, a separate Data Monitoring Committee was not required, in line with EMA guidelines (EMEA/CHMP/EWP/5872/03 Corr), as safety monitoring was provided throughout the study via continuous medical oversight from the Sponsor and the contract research organisation (CRO; Scope International AG, Mannheim, Germany, funded by the sponsor). This trial is registered with EudraCT (number 2011-002901-31) and ClinicalTrials.gov (number NCT01439100).

Role of the funding source

KR and AO (on behalf of the sponsor) initially discussed ideas for this study with CT. MH, KR, AO (on behalf of the sponsor) and the SSC (JD, MH, ML [on behalf of the sponsor] together with KRC, PM-M, OR and CT) worked on the design, development and conduct of the study. Data were collected by the investigators (CT, KRC, RE, MV, MS, AK-W, MJM; the study sponsor had no role in data collection). The study was monitored by the CRO, who also analysed the data (in accordance with the statistical analysis plan, developed by the sponsor- and non-sponsor-members of the SSC). All authors had full access to the study data, and sponsor- and non-sponsor members of the SSC contributed to the interpretation of the data. This article was developed by the sponsor- and non-sponsor authors in face-to-face meetings, telephone conversations and with support from a medical writer (funded by the sponsor). All sponsor- and non-sponsor authors were involved in the decision to submit the paper for publication. Several drafts were prepared and reviewed by all authors who approved the final submitted version. The corresponding author had final responsibility to submit the publication.

Results

Patients were recruited between 10 February 2012 and 5 November 2013. Of 202 patients randomised (OXN PR: n=93, placebo: n=109; the imbalance in randomisation resulted from sites recruiting small numbers of patients being unable to complete randomised blocks) 66·7% (n=62 of 93) receiving OXN PR and 70·6% (n=77 of 109) receiving placebo completed 16 weeks of double-blind treatment.

Discontinuations due to lack of efficacy were more common with placebo (14 of 109 patients; 12·8%) versus OXN PR (3 of 93 patients, 3·2%), while discontinuations due to adverse events were less common with placebo (10 of 109 patients; 9·2%) versus OXN PR (17 of 93 patients, 18·3%; Figure 2). In total, 145 of 151 patients (96·0%) entering the open-label phase completed an additional 4 weeks of treatment with OXN PR (Figure 2).

The FAP comprised 194 of 202 (96·0%) randomised patients (OXN PR: 88 of 93 [94·6%] patients, placebo n=106 of 109 [97·2%] patients) while the PPP comprised 176 of 202 (87·1%) randomised patients (OXN PR n=78 of 93 [83·9%] patients, placebo n=98 of 109 [89·9%] patients). Demographic and disease characteristics were balanced between treatment groups (Table 1).

The reduction in the primary endpoint of average 24-h pain score at Week 16 with OXN PR vs placebo was not statistically significant (FAP: OXN PR least squares [LS] mean [95% CI] 5·0 [4·5 to 5·5], placebo 5·6 [5·1 to 6·0]; LS mean difference [95% CI] -0·6 [-1·3 to 0·0]; p=0·058). A notable advantage of OXN PR vs placebo was also seen at Week 16 in the PPP pre-defined sensitivity analysis of the primary endpoint (-0·9 [-1·5 to -0·2]; p=0·010). However, due to the hierarchical testing used, confirmatory statistical testing ended at this point. Subsequent statistical inferential testing for the following secondary endpoints was only exploratory. Average 24-h pain scores were lower with OXN PR vs placebo at Week 4 (LS mean difference [95% CI] -0·6 [-1·1 to -0·1], p=0·018), Week 8 (-0·7 [-1·2 to -0·2], p=0·011) and Week 12 (-0·7 [-1·3, to -0·1], p=0·021) in the FAP (Figure 3). Responder rates (≥ 30% reduction from baseline) for average 24-h pain at Week 16 were 13·7% greater with OXN PR vs placebo in the FAP (42 of 88 patients [47·7%] vs 36 of 106 patients [34·0%]; p=0·021; PPP: 39 of 78 patients [50·0%] vs 30 of 98 patients [30·6%], p=0·003). Responder rates ('much improved' or 'very much improved') were numerically greater with OXN PR vs placebo for CGI-I (OXN PR 36·4% [32 of 88 patients] vs placebo 26·7% [28 of 105 patients], p=0·019).

Median (IQR) exposure to study drug was reflecting the 16-week double-blind treatment duration (OXN PR: 112 [79 to 113] days, placebo 112 [64 to 114] days). Mean (SD) daily dose of study medication was lower in the OXN PR cohort (18·8 [8·4] mg) compared with placebo (23·5 [8·9] mg). The average number of L-DOPA / benserazide hydrochloride 100/25 mg rescue medication tablets taken per day was slightly lower in the OXN PR group (0.3 (SD 0.43)) compared to placebo (0.4 (SD 0.61)), and the median (range) total overall use over the 16 weeks was also less with OXN PR (200·0 [0 to 19200] mg) versus placebo (500·0 [0 to 28100] mg).

In exploratory analyses, OXN PR and placebo groups were comparable for observed change from baseline to Week 16 in NMSS total score and domain scores (including no negative effect of OXN PR on gastrointestinal function [Table 2; NMSS domain and total scores at baseline are detailed in the supplementary appendix]), as well as scores for PDSS-2 (a similar low percentage of patients

receiving OXN PR and placebo suffered very often/often from distressing dreams or distressing hallucinations at night, see supplementary appendix), PDQ-8, EQ-5D-3L, HADS-depression and anxiety, CISI-PD, UPDRS part III and part IV and WOQ-9 (Table 3). Responder rates ('much improved' or 'very much improved') for PGI-I (OXN PR 37·5% [33 of 88 patients], placebo 26·7% [28 of 105 patients], p=0·022) at Week 16 were numerically greater with OXN PR vs placebo.

Post-hoc analysis revealed that the percentage of patients with severe pain decreased from baseline to Week 16 for all pain types in both treatment groups. In the subgroup of patients with severe musculoskeletal PD pain (King's PD Pain Scale: domain 1) at Week 16 OXN PR significantly improved pain compared with placebo (LS mean difference [95% CI] -0·9 [-1·7 to -0·1], p=0·023 [Baseline: OXN PR n=67, placebo n=77; Week 16 OXN PR n=44, placebo n=54]). Similar results were observed in patients with severe nocturnal pain (King's PD Pain Scale: domain 4: -1·6 [-2·7 to -0·4], p=0·010 [Baseline: OXN PR n=26, placebo n=37; Week 16 OXN PR n=18, placebo n=26]). There were no significant differences between treatment groups at Week 16 in other PD-related pain types. Notable improvements with OXN PR versus placebo were also in severe musculoskeletal pain and severe nocturnal types of PD pain in the subgroup of patients who provided assessment values at both baseline and Week 16 (LOCF; improvements in types of severe PD-related pain are detailed in the supplementary appendix).

During the open-label treatment phase with OXN PR, patients who had received placebo during double-blind treatment experienced a greater reduction in average 24-h pain scores (mean [SD] change -1·2 [1·5] points) compared with those who received OXN PR during double-blind treatment (-0·3 [1·0] points). This reflects higher mean (SD) average 24-h pain scores at the start of open-label treatment in the prior placebo group vs OXN PR group (5·5 [2·1] vs 4·7 [2·4]), further supporting the clinical beneficial analgesic effect of OXN PR.

During double-blind treatment, the overall incidences of all-causality adverse events, treatment-related adverse events and serious adverse events were similar between treatment groups (Table 4). Incidences of all-causality nausea (18 of 92 patients [19·6%] vs 13 of 109 patients [11·9%]), constipation (16 of 92 patients [17·4%] vs 6 of 109 patients [5·5%]), vomiting (7 of 92 patients [7·6%] vs 3 of 109 patients [2·8%]) and hyperhidrosis (7 of 92 patients [7·6%] vs 2 of 109 patients [1·8%]) were more frequent in patients treated with OXN PR vs placebo (Table 4). Treatment-related nausea (16 of 92 patients [17·4%] vs 10 of 109 patients [9·2%]) and treatment-related constipation (16 of 92 patients [17·4%] vs 6 of 109 patients [5·5%]) were notably higher with OXN PR vs placebo. Constipation was not reported as a SAE and resulted in study discontinuation in 2 of 92 patients (2·2%) and 0 of 109 patients randomised to OXN PR and placebo, respectively. During open-label treatment, the most frequent all-causality adverse events were nausea (12 of 151 patients, 7·9%), dizziness (11 of 151 patients, 7·3%) and fatigue (n=9 of 151 patients, 6·0%, for further details please see the supplementary appendix).

No clinically relevant changes in laboratory parameters were observed. Treatment-related adverse events concerning vital signs included hypotension (OXN PR n=3), orthostatic hypotension (placebo n=1), blood pressure decrease (placebo n=1), tachycardia (OXN PR n=1) and hypertension (OXN PR n=2, placebo n=2).

Discussion

The primary endpoint of improved average 24-h pain score with OXN PR vs placebo at Week 16 (FAP) was not met (p=0·058). However, the PPP analysis revealed that appropriate adherence resulted in significantly improved 24-h average pain scores at Week 16 with OXN PR vs placebo (p=0.010). Assessments of 24-h pain at other timepoints during the study in FAP also indicated OXN PR had a positive effect on severe PD-related pain: Week 4 (p=0.018), Week 8 (p=0·011) and Week 12 (p=0·021), although confirmatory statistical significance cannot be inferred due to the limitations of the hierarchical testing procedure. Other secondary endpoint data also favoured OXN PR, including greater responder rates for 24 h pain scores , 2·5-fold lower total use of L-DOPA rescue medication, and clinically relevant improvements in CGI-I and PGI-I versus placebo. Patients in the placebo group required higher doses of study medication and discontinued due to lack of efficacy more frequently compared with patients randomised to OXN PR, further supporting the beneficial effects of OXN PR.

Reasons for exclusion from the PPP, including intake of considerable amounts of L-DOPA rescue medication observed in the placebo group only, had a notable influence on the analysis results. This may be explained by motor fluctuations and dyskinesia-related pain being particularly responsive to dopaminergic therapy, compared with other PD pain types [1,32], although we tried to exclude purely 'off-period'-related pain. Improvement in pain over time, which is anticipated in severe pain, may also have contributed to the failure to meet the primary endpoint. As was observed in the placebo group, pain severity decreased over the course of the study. Severe PD-related pain was an inclusion criterion in this study, but it is unlikely that patients will tolerate severe pain for more than a few weeks. This may explain the drop-out rate and missing data at Week 16. Therefore, assessment of change in less severe pain may have better reflected the true treatment effect. In addition, the higher average daily dose of study medication observed in the placebo group may have influenced analgesic response.

The heterogeneity of PD pain types may also have impacted the outcome of this study. Specific pain-related symptom assessment using the King's PD Pain Scale, revealed that OXN PR was associated with particular improvements in severe musculoskeletal pain (p=0·023) and severe nocturnal pain (p=0·010), the two most common PD-related pain types observed at baseline. L-DOPA rescue medication, used at a higher total dose in the placebo group, may have influenced 'off-period'-pain and the associated findings in these patients. It is noteworthy that this study represents the first field testing of the King's PD Pain scale, and captures the heterogeneous nature of PD-related pain as previously identified [1,31]. In the validation study of the King's PD Pain Scale, highest pain scores compared with controls were observed in musculoskeletal and nocturnal pain domains [31]. The efficacy of the OXN PR in these pain domains in the present study supports the validity of the scale in this population.

Based on the pathophysiology and diversity of PD pain, it is likely a variety of management approaches are warranted. Nociceptive PD pain arises due to activation of nociceptors in non-neuronal tissue, while neuropathic PD pain results in part from basal ganglia dysfunction and dopaminergic denervation [8,11]. Patients with PD neuropathic pain have lower than normal pain thresholds and L-DOPA may play a role in pain modulating systems, acting on pain thresholds and

pain-induced cerebral activations [33,34]. However, observations that apomorphine has little effect on neuropathic pain processing suggests the importance of other systems [11,35]. Opioids and other analgesics with effects on the descending inhibitory pain pathways could therefore be effective against nociceptive and neuropathic pain [11]. Many patients experience a complex array of pain and in clinical practice it is important to distinguish 'off-period' pain, which can be effectively managed with dopaminergic therapy, from other types of PD pain to optimise treatment strategies.

Worsening of NMS with active treatment was not observed in this study. There were no negative effects on sleep, mood/cognition, sexual function and perceptual problems/hallucinations. Constipation, an anticipated side effect, given it affects many patients with PD and is a common class effect of opioid analgesics [15,16], was not particularly aggravated by OXN PR. Although as an adverse event constipation was more frequent with OXN PR vs placebo, it rarely resulted in discontinuation of study medication and in no case was it considered an SAE. These findings contrast other opioid studies, in which constipation is estimated to affect 80% of individuals; this difference may relate to the unique mechanism of action of OXN PR [18]. Other common adverse events observed were consistent with those documented with OXN PR in other pain settings, and included nausea, somnolence, dizziness and fatigue [36]. It is noteworthy that the mean daily dose of OXN PR during double-blind treatment (18·8 mg) was substantially lower than the highest dose of 120 mg/day permitted in other placebo-controlled, double-blind trials in patients with moderate-to-severe chronic pain [19,36].

Oxycodone is known to have addictive properties in common with all opioids and, as a Scheduled Drug, is subject to stringent controls and regulations on its prescription, storage and distribution. OXN PR combines oxycodone with the antagonist naloxone, which further reduces its potential for abuse [37]. In addition, this 16-week study found no evidence for PD patients increasing their mean OXN PR dose, indicating patients were not up-titrating to higher opioid doses or becoming addicted to oxycodone.

To our knowledge this is the first randomised, controlled trial specifically designed to investigate treatment of PD-related pain. One randomised, controlled trial of rotigotine with pain as a post-hoc analysis showed improvements in pain associated, which were attributed to benefits in motor function and sleep disturbances [38]. In addition, a small prospective study of PD patients demonstrated efficacy of OXN PR 10/5 mg for chronic pain [28]. As the first trial of its kind, the statistical methods are of an exploratory nature. While the p-values for the secondary endpoints are below 0·05, statistical significance could not be inferred due to the limitations of the hierarchical testing procedure.

The current study was limited by the restrictive inclusion criteria of very severe pain using a non-PD-specific pain scale. Lack of prior randomised controlled studies of PD-related pain hampered estimations of sample size and may have resulted in the trial being underpowered in terms of the margin of effect. Other limitations include L-DOPA as rescue medication, which may have impacted some types of PD-related pain, the imbalance in randomisation (OXN PR n=93, placebo n=109) and quantity of missing data. Also, intermittent (or incidental) off-period related pain could not be excluded as this may occur in any patient with fluctuating PD. Further studies of OXN PR for PD-related pain are warranted, including larger patient groups followed for a longer duration,

investigation of higher doses which reflect the prescribing information for OXN PR in chronic pain, and studies comparing the analgesia obtained from OXN PR with other treatments and non-pharmacologic interventions.

Research in Context

Evidence before this study

PubMed and Cochrane Database were searched up to July 2011 using the key words 'pain', 'Parkinson', and 'randomised controlled trial'. No placebo-controlled randomised trials were identified which were specifically designed to investigate the analgesic efficacy of opioids in patients with Parkinson's disease (PD)-related pain and no trials used assessment of pain as the primary endpoint for efficacy. These findings are in agreement with the publication *The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the non-motor symptoms of Parkinson's disease* published in 2011.

Added value of this study

A subsequent search of PubMed, conducted in May 2015 using the terms 'pain', 'Parkinson's' and 'randomi*' in titles/abstracts revealed one randomised, controlled trial with pain as a post-hoc endpoint, but no trials were identified with pain as a primary endpoint.

To our knowledge, this Phase II study is the first randomised, controlled trial specifically designed to investigate medical treatment of PD-related pain. While the primary endpoint was not met, secondary endpoint data indicate a potential utility of OXN PR in this setting, which requires further investigation in randomised, controlled trials. Assessment of pain types in this study was based on the first, validated scale for PD-related pain, and provides insight into the heterogeneity of PD pain as well as the types of PD-related pain for which OXN PR may have various positive effects. This study adds to the limited knowledge base of the efficacy and safety of opioid-based treatment of patients with PD suffering from complex pain. Since the submission of this paper, a study was published that supports the positive effects of OXN PR on PD-related pain, although this was limited by the open-label design and small (n=16) number of patients.

Implications of all available evidence

Effective diagnosis and management of PD-related pain is essential to lessen the burden of this disease. The results of this study increase the evidence-base for the management of PD-related pain and in particular will help to guide the design of future trials in this setting, and ultimately lead to improved management of PD-related pain.

Declarations of interest

CT reports personal fees from Mundipharma Research GmbH & Co. KG, during the conduct of the study, for being on the study steering committee; salary from Paracelsus-Elena-Klinik, Kassel, Germany, outside the submitted work. In addition, CT is one of the inventors of the patent WO 2012/089738. EuroCeltique is the licencee of this patent. Payment for Advisory Board from: Mundipharma Germany GmbH & Co. KG, Mundipharma Research GmbH & Co. KG, UCB, Vifor, Britannia, Novartis. Payment for Lectures from: UCB, Desitin, Britannia.

KRC reports personal fees from Mundipharma Research GmbH & Co. KG, during the conduct of the study, for being on the study steering committee; and funding from Parkinson's UK, honorarium for consultancy and Advisory Board attendance from Mundipharma Research GmbH & Co. KG and Mundipharma Germany GmbH & Co. KG and NAPP.

PM-M reports personal fees from Mundipharma Research GmbH & Co. KG, during the conduct of the study for being on the study steering committee. He received a Parkinson's UK Innovation Grant (INN-12D)-Support, as Researcher, for the development and validation of a specific rating scale for pain assessment in Parkinson's disease.

OR has received honoraria from Mundipharma Research GmbH & Co. KG, for being on the study steering committee. He received honoraria for being a member of advisory boards of: Mundipharma Germany GmbH, AbbVie, Britannia, Lundbeck, Merck, Mundipharma, Sanofi, Servier, Teva, UCB, XenoPort, Zambon.

RE has received honoraria for consultancy from: Mundipharma Research GmbH & Co. KG, Mundipharma Germany GmbH & Co. KG, Novartis, Teva Pharma, Neurotransdata GmbH, Desitin Arzneimittel GmbH, Kompetenznetz Parkinson, Pfizer, Abbvie, Boehringer-Ingelheim, Biogen, GE-Healthcare, Glaxo-Smithkline, MSD, Lichen Pharma, Medizinische Videobeobachtung/MVB, Merck, Merck Serono, Orion Pharma, Osmotica, Quanup, Schering Plough, UCB.

KR and AO are employees of Mundipharma Research GmbH & Co. KG.

JD and ML are employed by Mundipharma Research Limited.

MH is employed by Mundipharma Research GmbH & Co. KG and is one of the inventors of the patent WO 2012/089738. EuroCeltique is the licencee of this patent.

MS, AK-W, MJM, and MV have no conflicts of interest to declare.

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Disease Rating Scale, which was subsequently corrected. Publication management was undertaken by Dorothea Greifenberg (Mundipharma Research GmbH & Co. KG).

Contributors

MH, CT, KR and AO conceived and designed the study. KR, AO, JD, MH, ML, KRC, PM-M, OR and CT participated in the study steering committee and designed the study. CT, KRC, RE, MV, MS, AK-W, and MJM were study investigators and collected data. ML was responsible for the statistical analysis. All authors had full access to the data, interpreted the data, critically reviewed each draft of the manuscript and approved the final submitted version. The article was developed by the authors with support from a medical writer (SM) who incorporated the authors' feedback.

PANDA Study Group

Czech Republic: M Baláž, R Jech, P Kaňovský, L Pazdera, V Mach, D Roubcová, M Vališ, M Kuchar; *Germany*: C Trenkwalder, J Classen, D Dressler, R Ehret, S Muhlack, U Polzer, J Schwarz, M Sommer, J Kassubek, A Kühn, K Eggert, C Winkler, A Ceballos-Baumann, H Reichman; *Hungary*: A Csányi, A Folyovich, N Lévai, J Lajtos, M Sátori, M Zsolnai, L Vécsei; *Poland*: A Krygowska-Wajs, P Półrola, A Szczepańska-Szerej, A Honczarenko, A Kamińska, A Potemkowski, G Opala, A Klimek, M Rudzińska, *Romania*: V Albu, C Enache, C Falup-Pecurariu, C Mitu, A Roceanu; Spain: E Balaguer, J Garcia Moreno, G Linazasoro, M Martí Domenech, F Vivancos, J Kulisevsky, A Sesar, M Rodriguez; *UK*: K Chaudhuri, S Ellis, S Molloy, J Raw, K Amar, B Boothman.

Tables and figures

Table 1. Patient demographic and clinical characteristics at baseline (full analysis population)

	OXN PR N=88	Placebo N=106
Age, years; mean (SD)	66·7 (8·9)	67.5 (8·1)
Male / female, n (%)	43 (48·9) / 45 (51·1)	57 (53·8) / 49 (46·2)
MMSE score, mean (SD)	28·6 (1·5)	28·6 (1·5)
UPDRS score, mean (SD)		
Part III	30·9 (14)	30·7 (12)
Part IV	5·1 (3·6)	4·9 (3·8)
Hoehn and Yahr classification, n (%)		
Stage 2	20 (22·7)	33 (31·1)
Stage 2·5	27 (30·7)	33 (31·1)
Stage 3	35 (39·8)	28 (26·4)
Stage 4	6 (6·8)	12 (11·3)
Duration of PD, years; mean (SD)	6·9 (5·2)	6·7 (4·2)
Duration of PD pain, years; mean (SD)	3·4 (3·0)	3·4 (2·8)
Baseline current PD medication use		
Patients with ≥1 current PD medication	83 (94·3)	99 (93·4)
Anti-Parkinson Drugs	82 (93·2)	97 (91·5)
Dopaminergic Agents	82 (93·2)	97 (91·5)
PD-related pain characteristics		
Average 24-h pain score (0 = no pain to 10 = pain as bad as you can imagine); mean (SD)	7·3 (1·0)	7·3 (0·9)
Severe types of PD pain, n (%)[a]		
Musculoskeletal pain	67 (76·1)	77 (72·6)
PD-related chronic pain	19 (21·6)	27 (25·5)

Fluctuation-related pain	26 (29·5)	34 (32·1)
Nocturnal pain	26 (29·5)	37 (34·9)
Orofacial pain	2 (2·3)	6 (5·7)
Pain in limbs with discolouration	17 (19·3)	20 (18·9)
Patients currently receiving ≥1 PD pain medication, n (%)	64 (72·7)	74 (69·8)
Anti-inflammatory /antirheumatic agents	35 (39·8)	47 (44·3)
Other analgesic and antipyrectic agents	24 (27·3)	29 (27·4)
Dopaminergic agents	10 (11·4)	13 (12·3)

MMSE, mini mental state examination (score range 0–30; ≥27 indicates normal cognition); PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale (part III: motor examination [score range 0–56], part IV: complications of therapy in past week [score range 0–23], higher score indicates greater disability/complications)

[a]Assessed using the King's PD Pain Scale [31]

Table 2. Non-Motor Symptom Scale (NMSS, LOCF; Full Analysis Population)

Change in domain score: Baseline to Week 16	**OXN PR (N=88) Least Squares mean (95% CI)**	**Placebo (N=106) Least Squares mean (95% CI)**	**OXN PR vs placebo Least Squares mean difference (95% CI)**	**P value[b]**
Cardiovascular	0·1 (-0·5, 0·7)	0·1 (-0·4, 0·7)	-0·1 (-0·8, 0·7)	0·880
Sleep/fatigue	-3·0 (-4·5, -1·5)	-1·6 (-3·1, -0·2)	-1·4 (-3·0, 0·2)	0·077
Mood/cognition	-1·1 (-2·7, 0·5)	-1·3 (-2·8, 0·2)	0·2 (-2·1, 2·4)	0·887
Perceptual problems/hallucinations	0·3 (-0·1, 0·8)	0·1 (-0·4, 0·5)	0·3 (0·0, 0·5)	0·059
Attention/memory	-0·2 (-0·9,0·5)	-2·0 (-10·9, 0·4)	0·1 (-0·8, 1·0)	0·882
Gastrointestinal function[a]	-0·3 (-1·0, 0·3)	-0·7 (-1·3, -0·1)	0·3 (-0·5, 1·2)	0·407
Urinary function	-1·6 (-2·9, -0·2)	-0·7 (-2·0, 0·6)	-0·9 (-2·1, 0·3)	0·123
Sexual function	-0·4 (-1·0, 0·1)	-0·2 (-0·8, 0·3)	-0·2 (-1·0, 0·5)	0·590
Miscellaneous	-2·3 (-3·7, -1·0)	-2·1 (-3·4, -0·9)	-0·2 (-1·5, 1·2)	0·789
Total score	-8·6 (-13·5, -3·7)	-7·1 (-11·8, -2·5)	-1·5 (-6·9, 4·0)	0·593

NMSS domains were scored by multiplying the severity (rated as 0 = 'none' to 3 = 'severe') and frequency (rated as 1 = 'rarely' to 4 = 'very frequent') recorded for each item

[a]Includes Question 21: Does the patient suffer from constipation (bowel action <3 times weekly)?; mean (SD) change from baseline to Week 16 (LOCF) was OXN PR -0·1 (1·9), placebo -0·3 (2·3).

[b]Statistical testing was conducted on an exploratory basis only due to the hierarchical testing used

Table 3. Summary of findings for exploratory endpoints (LOCF; Full Analysis Population)

Change in score: Baseline to Week 16	**OXN PR (N=88) Least Squares mean (95% CI)**	**Placebo (N=106) Least Squares mean (95% CI)**	**OXN PR vs placebo Least Squares mean difference (95% CI)**	**P value**
PDSS-2 OXN PR n=88, placebo n=105	-6·2 (-8·2, -4·3)	-4·9 (-6·8, -3·1)	-1·3 (-3·5, 1·0)	0·258
PDQ-8 OXN PR n=76, placebo n=91	-6·5 (-9.3, -3·7)	-3·2 (-5·9. -0·6)	-3·3 (-6·7, 0·1)	0·060
EQ-5D-3L OXN PR n=76, placebo n=92	0·2 (0·1, 0·3)	0·1 (0·1, 0·2)	0·1 (0·0, 0·15)	0·057
HADS-anxiety[a] OXN PR n=80, placebo n=96	0·7 (0·2, 1·2)	0·0 (-0·5, 0·4)	0·7 (0·1, 1·3)	0·021
HADS-depression OXN PR n=80, placebo n=96	0·2 (-0·3, 0·7)	-0·2 (-0·6, 0·3)	0·3 (-0·3, 0·9)	0·267
CISI-PD OXN PR n=68, placebo n=90	-0·5 (-1·0, 0·1)	-0·4 (-0·9, 0·0)	-0·1 (-0·6, 0·5)	0·810
UPDRS part III[b] OXN PR n=88, placebo n=106	-2·7 (-4·5, -1·0)	-2·7 (-4·3, -1·2)	0·0 (-1·9, 2·0)	0·975
UPDRS part IV[b] OXN PR n=67, placebo n=90	-0·8 (-1·3, -0·2)	-0·3 (-0·8, 0·2)	-0·5 (-1·2, 0·1)	0·124

WOQ-9[c] OXN PR n=85, placebo n=104	71/85 (83·5%)[d]	89/104 (85·6%)[d]	0·9 (0·5, 1·6)	0·694

CISI-PD, Clinical Impression of Severity Index – Parkinson's disease; EQ-5D-3L, Euro-Quality of Life; HADS, Hospital Anxiety and Depression Scale; PDQ-8, Parkinson Disease Questionnaire-8; PDSS-2, Parkinson's Disease Sleep Scale-2; UPDRS, Unified Parkinson's Disease Rating Scale; WOQ-9, Wearing-Off Questionnaire.

[a]The small difference of 0.7 (3%) on a scale of 0 to 21 is not considered clinically relevant. [b]Part III: motor examination, Part IV: complications of therapy (includes dyskinesia, which was examined in a post-hoc analysis)

[c]Patients meeting WOQ-9 wearing off criteria (≥1 symptom in the WOQ-9 with improvement after the next dose of anti-Parkinsonian medication) at Week 16, odds ratio (95% CI)

[d]Data expressed as a percentage of evaluable patients

Table 4. Summary of adverse events occurring during double-blind treatment (safety population)

Adverse events and serious adverse events	**OXN PR (N=92) n (%)**	**Placebo (N=109) n (%)**
Adverse events		
Patients with ≥1 AE	60 (65·2)	76 (69·7)
Patients with ≥1 treatment-related AE[a]	52 (56·5)	62 (56·9)
Patients with ≥1 treatment-related severe AE[a]	6 (6·5)	5 (4·6)
Most frequent all-causality AEs[c]		
Nausea	18 (19·6)	13 (11·9)
Somnolence	12 (13·0)	15 (13·8)
Dizziness	12 (13·0)	12 (11·0)
Constipation	16 (17·4)	6 (5·5)
Fatigue	7 (7·6)	10 (9·2)
Headache	6 (6·5)	9 (8·3)
Dry mouth	5 (5·4)	5 (4·6)
Vertigo	6 (6·5)	4 (3·7)
Vomiting	7 (7·6)	3 (2·8)
Diarrhoea	2 (2·2)	7 (6·4)
Hyperhidrosis	7 (7·6)	2 (1·8)
Fall	5 (5·4)	3 (2·8)
Serious adverse events		
Patients with ≥1 SAE[b]	5 (5·4)	7 (6·4)
Number of SAEs	9	10
Patients with ≥1 treatment-related SAE[a]	2 (2·2)	2 (1·8)
SAEs[d]		
Atrial fibrillation	0	1 (0.9)

Benign prostatic hyperplasia	0	1 (0.9)
Cholelithiasis	1 (1.1)	0
Cystitis	1 (1.1)	0
Diarrhoea	0	1 (0.9)
Endometrial hypertrophy	0	1 (0.9)
Loss of consciousness	1 (1.1)	0
Lumbar spine stenosis	0	1 (0.9)
Melaena	1 (1.1)	0
Oedema (peripheral)	0	1 (0.9)
Osteoarthritis	0	1 (0.9)
Pain in extremity	0	1 (0.9)
Pancreatitis, acute	1 (1.1)	0
Pneumonia	0	1 (0.9)
Pyelocaliectasis	1 (1.1)	0
Pyelonephritis	1 (1.1)	0
Rib fracture	1 (1.1)	0
Spondylolisthesis	0	1 (0.9)
Urinary retention	1 (1.1)	0
Deaths		
Patients who died	0	0

AE, adverse event; SAE, serious adverse event

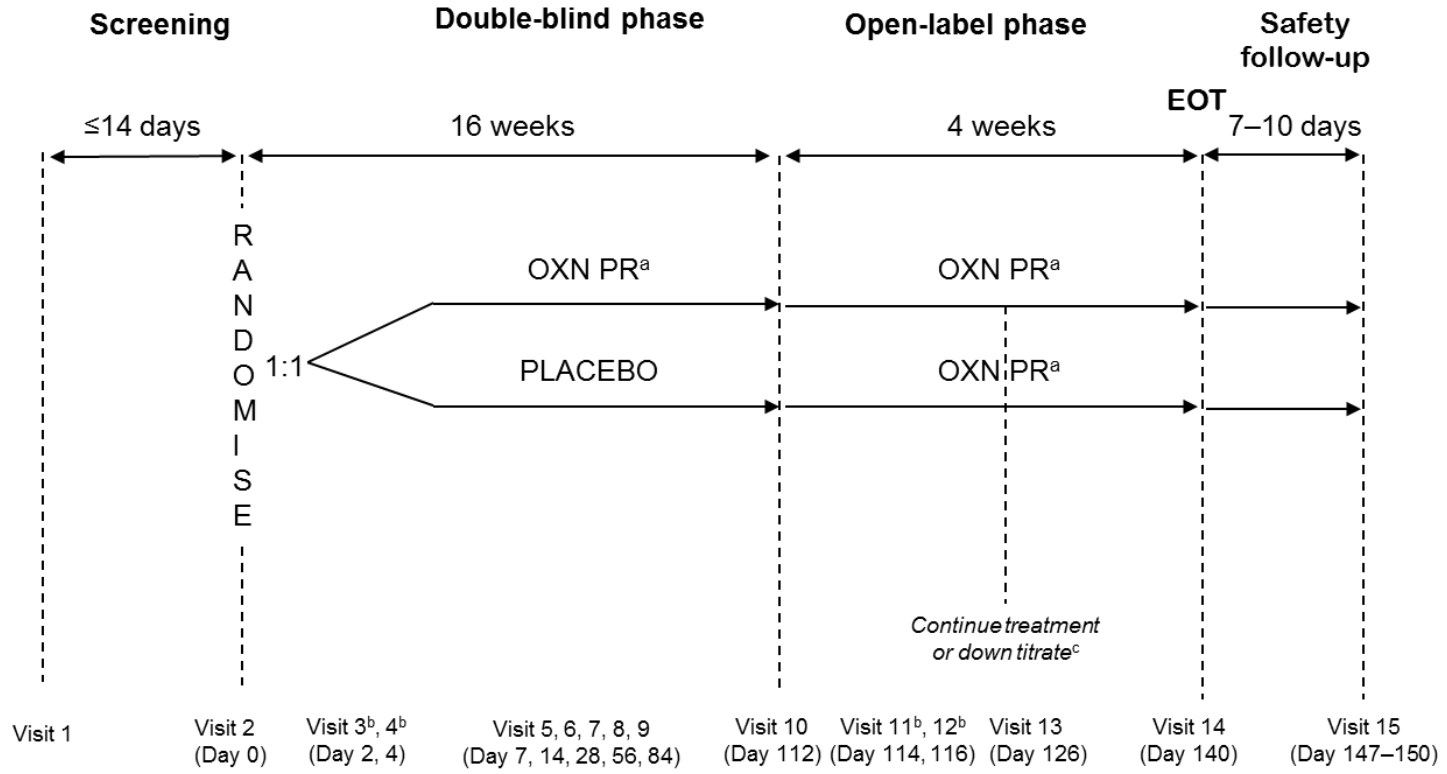
[a]Investigator considered the AE to be 'unlikely', 'possibly', 'probably', or 'definitely' related to study medication

[b]Twelve treatment-emergent SAEs were judged to be severe and all either recovered or recovered with sequelae with the exception of one case of atrial fibrillation which was ongoing in a patient receiving placebo

[c]AEs occurring ≥5% in either treatment group (MedDRA preferred term)

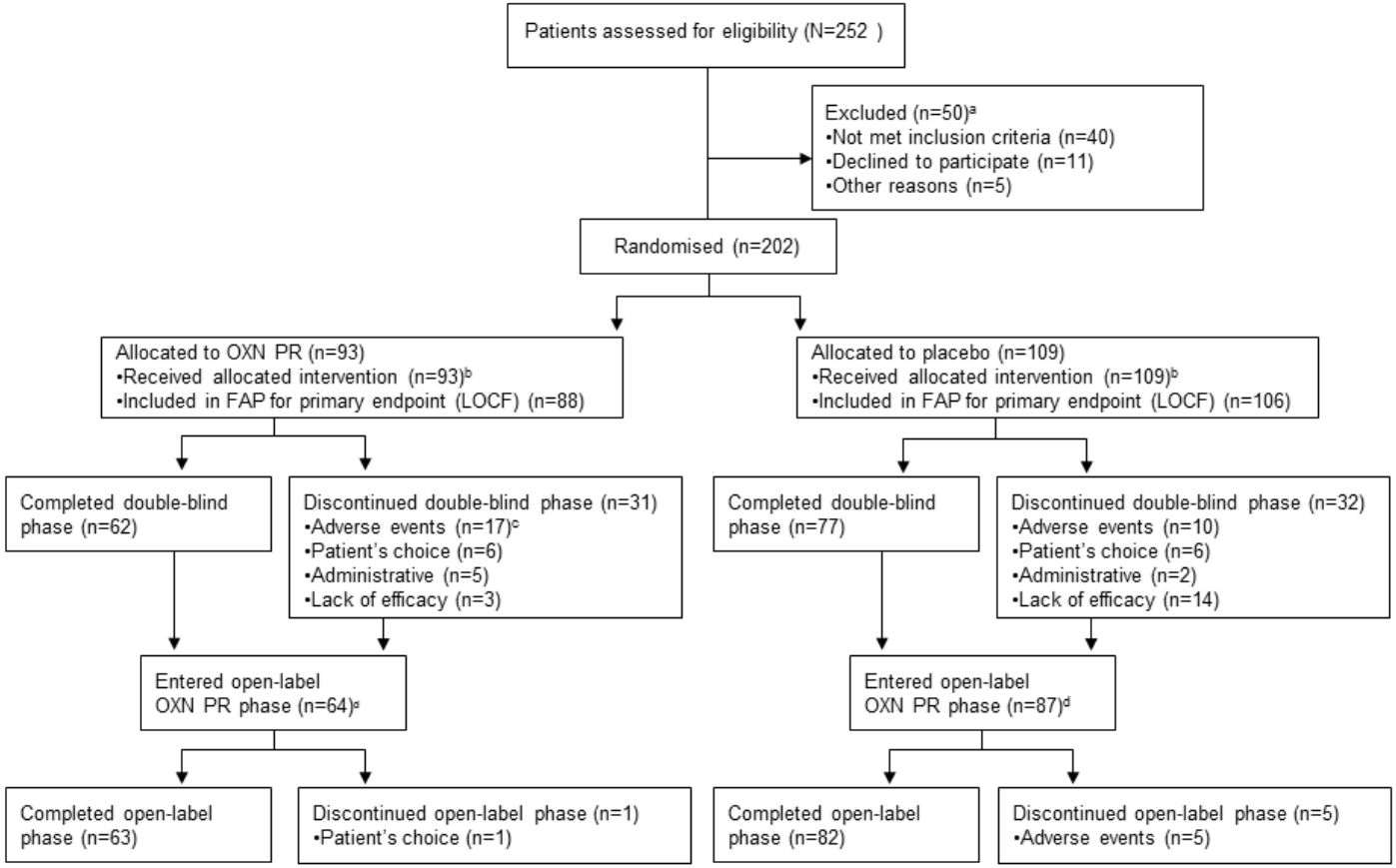
[d]AEs Patients may have reported >1 SAE (MedDRA preferred term)

Figure 1. Study design



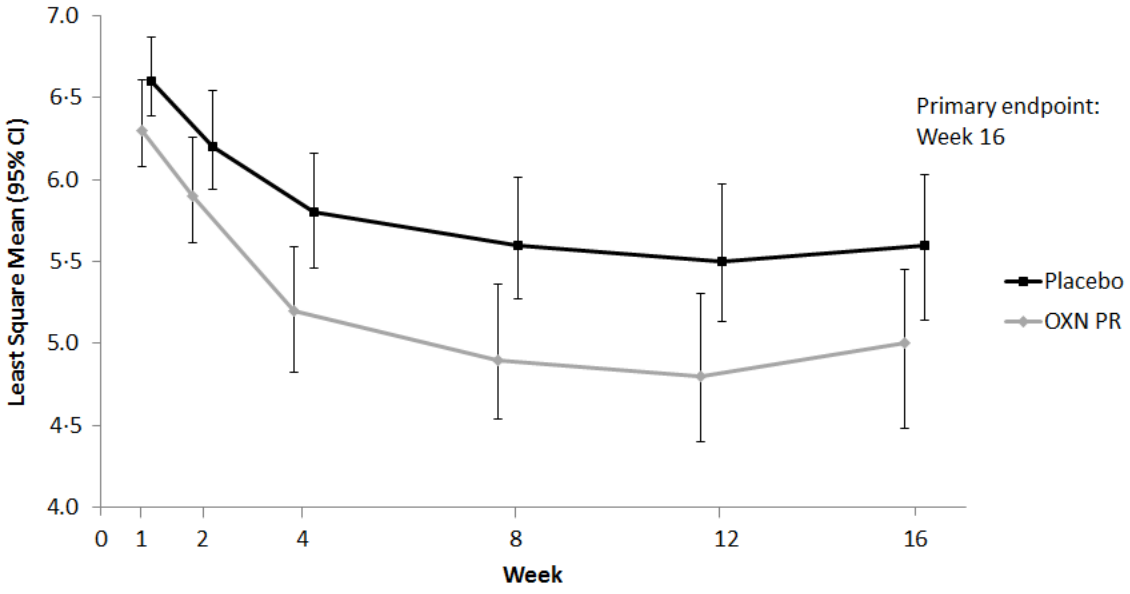
[a]Starting dose of OXN PR was 5 mg oxycodone/2.5 mg naloxone bid
[b]Telephone call (other visits were to study clinics)
[c]In order to terminate opioid treatment in the open-label phase, OXN PR was down titrated gradually over a period of ≤14 days
EOT, end of treatment, OXN PR, prolonged-release oxycodone/naloxone tablets
Additional unscheduled visits for titration of study medication were conducted as required

Figure 2. Patient disposition



[a]More than one reason for screening exclusions was provided for some patients
[b]Full analysis population comprised all randomised patients who received ≥1 dose of study medication and had ≥1 post-baseline primary efficacy endpoint measure
[c]One patient had no adverse events leading to discontinuations, but the reason given for discontinuation was 'adverse event'
[d]Patients who completed double-blind treatment or who discontinued prematurely but received ≥8 weeks of study treatment could enter the open-label phase
FAP, full analysis population; LOCF, last observation carried forwards; OXN PR, prolonged-release oxycodone/naloxone tablets

Figure 3. Average 24-h pain scores during double-blind treatment (MMRM, full analysis population)



OXN PR, n	88	87	80	70	68	61
Placebo, n	105	103	100	86	76	73

Average 24-h pain was assessed on an 11-point scale (0 = no pain to 10 = pain as bad as you can imagine)
MMRM, Mixed Model, Repeated Measures
Arithmetic mean (SD) scores at Baseline were OXN PR: 7·3 (1·0), placebo: 7·3 (0·9)

References

1. Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurol*. 2009;**8**:464-474.

2. Maass A, Reichmann H. Sleep and non-motor symptoms in Parkinson's disease. *J Neural Transm*. 2013;**120**:565-569.

3. Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. *Mov Disord*. 2011;**26**:399-406.

4. Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol*. 2006;**5**:235-245.

5. Rana AQ, Kabir A, Jesudasan M, Siddiqui I, Khondker S. Pain in Parkinson's disease: analysis and literature review. *Clin Neurol Neurosurg*. 2013;**115**:2313-2317.

6. Negre-Pages L, Regragui W, Bouhassira D, Grandjean H, Rascol O. Chronic pain in Parkinson's disease: the cross-sectional French DoPaMiP survey. *Mov Disord*. 2008;**23**:1361-1369.

7. Beiske AG, Loge JH, Ronningen A, Svensson E. Pain in Parkinson's disease: Prevalence and characteristics. *Pain*. 2009;**141**:173-177.

8. Wasner G, Deuschl G. Pains in Parkinson disease: many syndromes under one umbrella. *Nat Rev Neurol*. 2012;**8**:284-294.

9. Defazio G, Berardelli A, Fabbrini G et al. Pain as a nonmotor symptom of Parkinson disease: evidence from a case-control study. *Arch Neurol*. 2008;**65**:1191-1194.

10. Brefel-Courbon C, Grolleau S, Thalamas C et al. Comparison of chronic analgesic drugs prevalence in Parkinson's disease, other chronic diseases and the general population. *Pain*. 2009;**141**:14-18.

11. Perez-Lloret S, Rey MV, Dellapina E, Pellaprat J, Brefel-Courbon C, Rascol O. Emerging analgesic drugs for Parkinson's disease. *Expert Opin Emerg Drugs*. 2012;**17**:157-171.

12. Seppi K, Weintraub D, Coelho M et al. The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the non-motor symptoms of Parkinson's disease. *Mov Disord*. 2011;**26 Suppl 3**:S42-S80.

13. Vargas-Schaffer G. Is the WHO analgesic ladder still valid? Twenty-four years of experience. *Can Fam Physician*. 2010;**56**:514-515.

14. Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE 1). *Pain Med*. 2009;**10**:35-42.

15. Kaye J, Gage H, Kimber A, Storey L, Trend P. Excess burden of constipation in Parkinson's disease: a pilot study. *Mov Disord*. 2006;**21**:1270-1273.

16. Brock C, Olesen SS, Olesen AE, Frokjaer JB, Andresen T, Drewes AM. Opioid-induced bowel dysfunction: pathophysiology and management. *Drugs*. 2012;**72**:1847-1865.

17. Smith K, Hopp M, Mundin G et al. Low absolute bioavailability of oral naloxone in healthy subjects. *Int J Clin Pharmacol Ther*. 2012;**50**:360-367.

18. Smith K, Hopp M, Mundin G et al. Naloxone as part of a prolonged release oxycodone/naloxone combination reduces oxycodone-induced slowing of gastrointestinal transit in healthy volunteers. *Expert Opin Investig Drugs*. 2011;**20**:427-439.

19. Ahmedzai SH, Nauck F, Bar-Sela G, Bosse B, Leyendecker P, Hopp M. A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain. *Palliat Med*. 2012;**26**:50-60.

20. Ahmedzai SH, Leppert W, Janecki M et al. Long-term safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate-to-severe chronic cancer pain. *Support Care Cancer*. 2015;**23**:823-830.

21. Dunlop W, Uhl R, Khan I, Taylor A, Barton G. Quality of life benefits and cost impact of prolonged release oxycodone/naloxone versus prolonged release oxycodone in patients with moderate-to-severe non-malignant pain and opioid-induced constipation: a UK cost-utility analysis. *J Med Econ*. 2012;**15**:564-575.

22. Koopmans G, Simpson K, De AJ, Lux EA, Wagemans M, Van MY. Fixed ratio (2:1) prolonged-release oxycodone/naloxone combination improves bowel function in patients with moderate-to-severe pain and opioid-induced constipation refractory to at least two classes of laxatives. *Curr Med Res Opin*. 2014;**30**:2389-2396.

23. Löwenstein O, Leyendecker P, Hopp M et al. Combined prolonged-release oxycodone and naloxone improves bowel function in patients receiving opioids for moderate-to-severe non-malignant chronic pain: a randomised controlled trial. *Expert Opin Pharmacother*. 2009;**10**:531-543.

24. Sandner-Kiesling A, Leyendecker P, Hopp M et al. Long-term efficacy and safety of combined prolonged-release oxycodone and naloxone in the management of non-cancer chronic pain. *Int J Clin Pract*. 2010;**64**:763-774.

25. Simpson K, Leyendecker P, Hopp M et al. Fixed-ratio combination oxycodone/naloxone compared with oxycodone alone for the relief of opioid-induced constipation in moderate-to-severe noncancer pain. *Curr Med Res Opin*. 2008;**24**:3503-3512.

26. Vondrackova D, Leyendecker P, Meissner W et al. Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. *J Pain*. 2008;**9**:1144-1154.

27. Trenkwalder C, Benes H, Grote L et al. Prolonged release oxycodone-naloxone for treatment of severe restless legs syndrome after failure of previous treatment: a double-blind,

randomised, placebo-controlled trial with an open-label extension. *Lancet Neurol*. 2013;**12**:1141-1150.

28. Madeo G, Schirinzi T, Natoli S et al. Efficacy and safety profile of prolonged release oxycodone in combination with naloxone (OXN PR) in Parkinson's disease patients with chronic pain. *J Neurol*. 2015;**Epub ahead of print**:DOI: 10.10007/s00415-015-7823-3.

29. Dworkin RH, Turk DC, Farrar JT et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;**113**:9-19.

30. Chaudhuri KR, Odin P, Antonini A, Martinez-Martin P. Parkinson's disease: the non-motor issues. *Parkinsonism Relat Disord*. 2011;**17**:717-723.

31. Chaudhuri KR, Rizos A, Truyers C et al. King's Parkinson's Disease (PD) Pain Scale, the first scale for pain in PD: An international validation. *Mov Disord*. 2015;**Epub ahead of print**:doi: 10.1002/mds.26270.

32. Ha AD, Jankovic J. Pain in Parkinson's disease. *Mov Disord*. 2012;**27**:485-491.

33. Brefel-Courbon C, Ory-Magne F, Thalamas C, Payoux P, Rascol O. Nociceptive brain activation in patients with neuropathic pain related to Parkinson's disease. *Parkinsonism Relat Disord*. 2013;**19**:548-552.

34. Brefel-Courbon C, Payoux P, Thalamas C et al. Effect of levodopa on pain threshold in Parkinson's disease: a clinical and positron emission tomography study. *Mov Disord*. 2005;**20**:1557-1563.

35. Dellapina E, Gerdelat-Mas A, Ory-Magne F et al. Apomorphine effect on pain threshold in Parkinson's disease: a clinical and positron emission tomography study. *Mov Disord*. 2011;**26**:153-157.

36. Löwenstein O, Leyendecker P, Lux EA et al. Efficacy and safety of combined prolonged-release oxycodone and naloxone in the management of moderate/severe chronic non-malignant pain: results of a prospectively designed pooled analysis of two randomised, double-blind clinical trials. *BMC Clin Pharmacol*. 2010;**10**:12.

37. DePriest AZ, Miller K. Oxycodone/Naloxone: role in chronic pain management, opioid-induced constipation, and abuse deterrence. *Pain Ther*. 2014;**3**:1-15.

38. Kassubek J, Chaudhuri KR, Zesiewicz T et al. Rotigotine transdermal system and evaluation of pain in patients with Parkinson's disease: a post hoc analysis of the RECOVER study. *BMC Neurol*. 2014;**14**:42.